**UNITED STATES ENVIRONMENTAL PROTECTION AGENCY**

WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

March 28, 2002

MEMORANDUM

FROM: Kathryn Boyle, CoChair IIFG

and

Kerry Leifer, CoChair IIFG

TO: Robert Forrest, Chief
Minor Use, Inerts, and Emergency Response Branch

SUBJECT: February 26 Meeting of the IIFG
Decision Memo

Please find attached the Inert Ingredient Focus Group recommendations for the inert ingredients associated with acetic acid and the citric acid cycle grouping.

INERT INGREDIENT FOCUS GROUP

DECISION DOCUMENT for

Acetic Acid and Salts

Citric Acid Cycle Chemicals and Salts

**Petition No.:** no

**Tolerance Reassessments?:** yes

**Common Chemical Names:** acetic acid, sodium acetate, citric acid, sodium citrate, potassium citrate, calcium citrate, malic acid, and fumaric acid

**Chemical Category/Group:** organic acids and their salts

**CAS. Reg. No.:** in tables

**HPV Chemical?** yes **Data Posted?** yes

**Use Pattern (pesticidal):** Citric acid and malic acid are FIFRA 25(b) active ingredients. As an active ingredient, citric acid is used as a disinfectant, sanitizer, fungicide and scale remover for use in toilets and food processing equipment. Both citric acid and fumaric acid are in 40 CFR 180.2. Acetic acid and citric acid are used in food-contact surface sanitizing solutions. As an active ingredient acetic acid is used on rights of ways, golf courses, open spaces, driveways and industrial sites at concentrations similar to that in vinegar to dessicate (dry out) plants.

**Use Pattern (non-pesticidal):** These are naturally occurring chemicals, food acids that are found in a wide variety of unprocessed foods, especially fruits. FDA clearances exist for these chemicals allowing their use in candy, jelly, ice cream, cakes, cookies, pies, soft drinks, fruit drinks, cheese, and animal drugs and feeds. Malic acid is a flavoring agent. Fumaric acid is an antioxidant and can be a component of adhesives. Citric acid can be used in various cleaners and strippers.

## 1. Physical/Chemical Properties:

| Table 1. Chemical Properties of Acetic Acid and Salts | | | | | |
|---|---|---|---|---|---|
| Chemical Property | Acetic Acid | Acetic Acid, Calcium salt | Acetic Acid, Magnesium salt | Acetic Acid, Potassium salt | Acetic Acid, Sodium salt |
| Vapor Pressure (mmHg) | 11.4 @ 20°C | 14.7 @25°C | NA | $7.08 \times 10^{-7}$ @25°C | $7.08 \times 10^{-7}$ @25°C |
| Log Kow | -0.17 | -0.97 | NA | -3.72 | -3.72 |
| Kd's (Koc) | 0.65 (228) Clastic mud 0.085 (6.5) muddy sand 0.046 (27) carbonate sand | NA | NA | NA | NA |
| Water Solubility (g/L) | 50 @20°C | 430 @25°C | very soluble | 2530 @25°C | 365 @20°C |
| pKa | 4.76 @25°C | NA | NA | NA | NA |
| Photodegradation | 50% after 21 days | NA | NA | NA | 6.6% after 17h |
| Biodegradation | 99% after 7 days using AS * | Readily biodegrades | NA | NA | 100% after 5 days using AS |
| Fish Acute Toxicity (96h-$LC_{50}$) | 75mg/L (Lowest value - Bluegill sunfish) | NA | NA | >6100mg/L (rainbow trout) | 100mg/L (zebra fish) |
| *Daphnia* Acute Toxicity | 65mg/L (48h-$EC_{50}$) | NA | NA | 7170mg/L (24h-$LC_{50}$) | >1000mg/L (48h-$EC_{50}$) |
| Algae Toxicity | 4000mg/L (8-day growth inhibition) | NA | NA | NA | 2460mg/L after 60-h growth inhibition) |
| Mammal Acute Oral ($LD_{50}$) | 4960 mg/kg-bw (mouse) | 4280mg/kg-bw (rat) | 8610mg/kg-bw (rat) | 3250mg/kg-bw (rat) | 3530mg/kg-bw (rat) |

* AS: Activated Sludge.

| Table 2. Chemical Properties of Citric Acid and Salts | | | | |
|---|---|---|---|---|
| Chemical Property | Citric Acid | Citric Acid, Sodium salt | Citric Acid, Tripotassium salt | Citric Acid, Trisodium salt |
| Vapor Pressure (mmHg@25°C) | $3.7x10^{-9}$ @25°C | NA | NA | $2.09x10^{-12}$ @25°C |
| Log Kow | -1.72 | NA | NA | -0.28 |
| Water Solubility (g/L @25°C) | 1330 @20°C | NA | NA | ~425 @25°C |
| pKa | pK1: 3.13; pK2: 4.76; pK3: 6.4 | NA | NA | NA |
| Photodegradation | NA | NA | NA | NA |
| Biodegradation | 98% after 48-h using domestic sewage | NA | NA | 90% after 48-h using AS |
| Fish Acute Toxicity (96h-$LC_{50}$) | 1516mg/L (Bluegill sunfish) | NA | NA | >18000-32000mg/L (guppy) |
| *Daphnia* Acute Toxicity | 120mg/L (72h-$EC_{50}$) | NA | NA | 5600-10000mg/L (48h-$EC_{50}$) |
| Algae Toxicity | 640mg/L 8-day growth inhibition) | NA | NA | >18000-32000mg/L (96h-$EC_{50}$) |
| Mammal Acute Oral | 5790mg/kg-bw (mouse) | 7100mg/kg-bw (mouse) | NA | NA |

| Table 3. Chemical Properties of Fumaric and Malic Acid | | |
|---|---|---|
| Chemical Property | Fumaric Acid | Malic Acid |
| Vapor Pressure (mmHg@25°C) | $1.54x10^{-4}$ | $4.6x10^{-6}$ |
| Log Kow | 0.33 @23°C | -1.26 |
| Water Solubility (g/L @25°C) | 7 | 592 |
| pKa | pK1: 3.02; pK2:4.46 @18°C | pK1: 3.4; pK2: 5.05 |
| Photodegradation | 50% degradation after 7.3h | 50% degradation after 2 days |

| | | |
|---|---|---|
| Biodegradation | 98% after 21 days using domestic sewage | readily biodegrades |
| Fish Acute Toxicity | 245mg/L (48h-$LC_{50}$ - zebra fish)) | NA |
| *Daphnia* Acute Toxicity | 212 mg/L (48h-$EC_{50}$) | 240mg/L (48h-$EC_{50}$) |
| Algae Toxicity | 41mg/L (72h-$EC_{50}$ - green algae) | NA |
| Rat Acute Oral | 9300mg/kg-bw (female rat) | 1600-3200mg/kg-bw (mouse, rat) |

## 2. Introduction:

Acetic acid is produced in biological tissues by fermentation of carbohydrates and also by organic synthesis. Vinegar which is a 5 to 8 % solution of acetic acid, is also a commonly consumed food.

Citric acid is widely distributed in plants and animals and occurs naturally in foods such as citrus fruits and tomatoes in substantial quantities. It is also one of the most widely used food additives. As a dietary supplement, calcium citrate is a source of calcium.

Malic acid occurs naturally as the major acid in apples, apricots, cherries, carrots and other foods. It is also used as a flavor booster in candy, jelly fruit drinks and ice cream.

Fumaric acid occurs in apples, beans, and carrots. It is commonly used to control pH and produce light textures in such foods as cake and cookies.

The following information was used in performing this assessment: The available information consisted of information retrieved from various websites, such as,

- EPA (www.epa.gov),
- NIOSH, (www.cdc.gov/niosh/ipcsneng/neng0000.html) and (www.cdc.gov/niosh/npg/npg.html)
- TOXNET ( www.toxnet.nlm.nih.gov.),
- NTP (ntp-server.niehs.nih.gov.),

Additional information included the information submitted to EPA's High Production Volume Challenge Program "Assessment Plan and Robust Summaries for the Acetic Acid and Salts Category." (Submitted June 28, 2001) Citric acid was also previously evaluated by the Agency in 1992 in the Citric Acid RED. Information identified as MRID was submitted to the Agency in support of citric acid as an active ingredient.

Acetic acid, calcium citrate, citric acid, sodium acetate, and sodium citrate have also been

evaluated by the Food and Drug Administration (FDA). They are FDA-affirmed GRAS (Generally Regarded As Safe). Calcium acetate is also FDA-affirmed GRAS (21 CFR 184.1185). Fumaric acid is approved for use as a direct and indirect food additive "at a level not in excess of the amount reasonably required to accomplish the intended effect."

International Safety Cards gave the following information on acetic acid (aqueous form): It is a colorless liquid and a weak acid. The substance and the vapor are corrosive to the eyes, the skin and the respiratory tract. There may be effects on the gastrointestinal tract. The TLV (Threshold Limit Value) is 25 mg/m3 or 10 ppm. Pure acetic acid is a solid below 62 $^{o}$F. It's most concentrated from is known as glacial acetic acid.

According to the International Safety Cards available for the other chemicals discussed in this document, they are all solids (granules, crystalline powder or flakes). No TLVs have been established.

**3. The Citric Acid Cycle:**

Citric acid, malic acid and fumaric acid are produced during the Citric Acid Cycle, which is also known as the Krebs Cycle. This cycle is essential for the metabolism of glucose and other simple sugars. The cycle consists of a series of enzymatic chemical reactions. These processes occur within the cell and are responsible for the final breakdown of food molecules to form carbon dioxide, water, and energy. For risk assessment purposes an important feature of this cycle is that these acids are used over and over again, thus giving the body an effective means of processing any ingested citric, fumaric, or malic acid.

**4. Role of the Cation**

Generally, in dealing with any acid salt, dissociation yields the anion from the acid and a cation. Generally, concerns for human and ecological health would stem from the acid moiety. Cations such as sodium, potassium, magnesium and calcium. are all minerals and required for proper functioning of biological systems. For risk assessment purposes an important feature of these minerals is that the body does have an effective means of processing them..

Sodium is necessary for the nerves and muscles to function properly. It is the principal cation of extracellular fluid, and helps to maintain the body's water balance. These electrolytes, the electrically charged ions in the body fluids, consist to a great extent of sodium and potassium.

Potassium is important in regulating blood pressure, regulating cellular water content, maintaining proper pH balance, and transmission of nerve impulses. It helps to regulate the electrical activity of the heart and muscles.

Calcium is necessary for bone and teeth formation. It is also important to the proper functioning of nerves, enzymes, and muscles, and plays a role in blood clotting and the

maintenance of cell membranes.

Magnesium is also used in building bones. It plays a role in releasing energy from muscles and regulating body temperature.

## 5. Toxicological Profile Table

Table 4a: Acute Toxicological Profile: acetic acid and sodium acetate

| Chemical | CAS No. | Acute Oral $LD_{50}$ | Acute Dermal $LD_{50}$ | Acute Inhalation $LD_{50}$ | Skin Irritation | Eye irritation |
|---|---|---|---|---|---|---|
| **Acetic acid** | 64-19-7 | $LD_{50}$ 10% solution:: 3530 mg/kg (MRID No. 99320)<br><br>$LD_{50}$ Rat: 3000mg/kg to 3800 mg/kg (MRID No. 33062)<br><br>$LD_{50}$ Mice: 4400 to 5600mg/kg (MRID No. 33062)<br><br>LDLo Rabbit:600 mg/kg | $LD_{50}$ : Rat 1.05mL/kg (MRID No. 99320)<br><br>LDLo Rabbit: 1060 uL/kg | LCLo: Rat 16000ppm/ 4 hours<br>$LD_{50}$ Mice:5620 ppm/1 hour | Human: 50 mg/24 hours: Mild<br>Rabbit: 50 mg/24 hours: Mild<br>Public literature indicates strong skin irritation<br><br>Human skin sensitization has occurred to concentrated acetic acid | Public literature indicates strong eye irritation |
| **Sodium acetate** | 127-09-3 | $LD_{50}$ Rat: 3500 mg/kg<br><br>$LD_{50}$ Mouse: 4960 mg/kg | Not available | Not available | Not available | Applied continuously for 3 hours to rabbit eyes at 0.1 M: No disturbance of the cornea |

| Table 4b: Toxicological Profile: acetic acid and sodium acetate | | | | | |
|---|---|---|---|---|---|
| **Chemical** | **CAS No.** | **Subchronic/ Chronic Toxicity** | **Developmental/ Reproductive Toxicity** | **Genetic Toxicity** | **Other Relevant Information** |
| **Acetic acid** | 64-19-7 | 0.5% acetic acid in drinking water for 2-4 months reduced the food intake of rats (MRID no. 33062)<br><br>Grastric lesions were noted in rats fed 4500 mg/kg acetic acid for 30 days. (MRID No.. 33062) | Apple cider vinegar (5% acetic acid) was administered to pregnant mice, rats, and rabbits up to 1600 mg/kg from GD 6-15–mice and rats; GD 6-18–rabbits. No abnormalities were observed (MRID No.. 90747). | Ames test (With and without activation; Strains TA100, TA1535, TA97, TA98, TA102; Zeiger et al, 1992): Negative | NIOSH has estimated that 595,000 workers are potentially exposued to acetic acid in the US<br><br>Detected in 2/12 human milk samples (Pellizzari et al, 1982)<br><br>OSHA: 10 ppm per 8 hr duration.<br><br>NIOSH: 10 ppm per 8 hr duration. 15 ppm per 15 min duration. 50 ppm considered 'immediately dangerous to life or health'<br><br>FDA: GRAS (maximum limits listed in 21CFR184.1005) |
| **Sodium acetate** | 127-09-3 | Not available | 1. In vitro studies suggest not teratogenic (ToxNet; MRID No. 33062)<br><br>2. Kavlock et al (1987). CD1 mice dosed via gavage at 1000 mg/kg/day from GD8-12. No adverse effects seen. | Sister chromatid exchange:negative<br><br>Negative: Ames test (With and without activiation Strains TA1535, TA1537, TA1538 and D4, MRID no. 33076) | FDA-affirmed GRAS: 21 CFR 184.1721 (not to exceed current good manufacturing practice) |

| Table 5a: Acute Toxicological Profile: citric acid and salts | | | | | | |
|---|---|---|---|---|---|---|
| **Chemical** | **CAS No.** | **Acute Oral $LD_{50}$** | **Acute Dermal $LD_{50}$** | **Acute Inhalation $LD_{50}$** | **Skin Irritation** | **Eye irritation** |
| **Citric acid** | 77-92-9 | $LD_{50}$ (mouse) 5040 mg/kg<br>LDLo (rabbit) 7000 mg/kg | Not available | Not available | Rabbit: 500 mg/24 Hours:<br>Miild | Rabbit: 700 ug/24 Hours:<br>Severe |
| **Calcium citrate** | 7693-13-2 | Not available | Not available | Not available | Not available | Not available |
| **Potassium citrate** | 866-84-2 | | | | | |
| **Sodium citrate** | 68-04-2 (anhydrous)<br>6132-04-3 (dihydrate)<br>6858-44-2 (penta-hydrate) | Not available | Not available | Not available | Not available | Not available |

| Table 5b: Toxicological Profile: citric acid and salts | | | | | |
|---|---|---|---|---|---|
| **Chemical** | **CAS No.** | **Subchronic/ Chronic Toxicity** | **Developmental/ Reproductive Toxicity** | **Genetic Toxicity** | **Other Relevant Information** |
| **Citric acid** | 77-92-9 | Not available | Not available | Ames test (With and without activation; Strains TA100, TA97, TA98, TA104; Al-Ani and Al-Lami et al, 1988): Negative | FDA-affirmed GRAS: 21 CFR 184.1033 (no limitation) |

| Chemical | CAS No. | Subchronic/ Chronic Toxicity | Developmental/ Reproductive Toxicity | Genetic Toxicity | Other Relevant Information |
|---|---|---|---|---|---|
| **Sodium citrate** | 68-04-2 (anhydrous)<br><br>6132-04-3 (dihydrate)<br><br>6858-44-2 (penta-hydrate) | Not available | In vitro studies suggest not teratogenic | Negative: Ames test (With and without activiation Strains TA97, TA102) | FDA-affirmed GRAS: 21 CFR 184.1751 (no limitation) |
| **Potassium citrate** | 866-84-2 | | | | |
| **Calcium citrate** | 7693-13-2 | Not available | Not available | Ames test (With and without activation; Strains TA97, TA98TA102 TA104; Fujita et al, 1988): Negative | FDA-affirmed GRAS: 21 CFR 184.1195 (no limitation) (may be used in infant formula) |

| Table 6a: Acute Toxicological Profile: fumaric acid | | | | | | |
|---|---|---|---|---|---|---|
| **Chemical** | **CAS No.** | **Acute Oral $LD_{50}$** | **Acute Dermal $LD_{50}$** | **Acute Inhalation $LD_{50}$** | **Skin Irritation** | **Eye irritation** |
| **Fumaric acid** | 110-17-8 | $LD_{50}$ Rat: 6800-10,700 mg/kg<br><br>$LD_{50}$ Mouse: 5000 mg/kg<br><br>LDLo Rabbit: 5000 mg/kg | Not available | Not available | Rabbit: 500 mg/24 Hours: Mild | Rabbit: 100 mg/24 Hours: Moderate |

| Table 6b: Toxicological Profile: fumaric acid | | | | | |
|---|---|---|---|---|---|
| **Chemical** | **CAS No.** | **Subchronic/ Chronic Toxicity** | **Developmental/ Reproductive Toxicity** | **Genetic Toxicity** | **Other Relevant Information** |
| **Fumaric acid** | 110-17-8 | 1. Co-administration with a naphthyridine derivative resulted in *fewer* stomach and lung tumors.<br><br>2. Co-injection with aflatoxin B1 *reduced* nuclear degeneration of hepatocytes<br><br>3. Tumor inhibition study: 1% in mouse diet for 48WK following 88 WK of thioacetamide treatment. Reduced incidence | In vitro studies suggest not teratogenic | 1. Mouse lymphoma (with and without activation): Positive at 2856-8000 µg/ml.<br><br>2. Ames test (With and without activiation; Strains TA97, TA98, TA100, TA102, TA1535) | FDA: Direct and indirect food additive<br><br>"At a level not in excess of the amount reasonably required to accomplish the intended effect." |

## 6. FDA-Sponsored Developmental Toxicity Studies

These studies were performed by the Food and Drug Research Laboratories in the 1970's. They have not been reviewed by the Agency, but were reported in the HPV submission.

Acetic Acid

At the highest dose tested (1600 mg/kg/day) in the mouse, the rat, and the rabbit, there were no effects on nidation (fertilization), or on maternal or fetal survival.

Malic Acid

At the only dose tested (350 mg/kg/day) in the rat, there were no treatment-related fetal or maternal toxic effects. No increases in fetal malformations were observed.

At the only dose tested (266 mg/kg/day) in the mouse, there were no treatment-related fetal or maternal toxic effects. No increases in fetal malformations were observed.

Citric Acid

At the only dose tested (241 mg/kg/day) in the rat, there was no indication of adverse effects on nidation, maternal, or fetal survival..

## 7. Hazard Characterization:

There is no available information on any of the chemicals considered in this document indicative of a hazard, significant adverse effects, to the general public or any population subgroup. These chemicals are naturally occurring and are part of human metabolic activity.

## 8. Type of risk assessment: qualitative

## 9. Sensitivity of Infants and Children:

These chemicals have low toxic potential. In addition, humans of all ages are highly exposed to them from natural and anthropogenic sources. At this time, there is no concern for potential sensitivity to infants and children. A safety factor analysis has not been used to assess the risk. For the same reasons the additional tenfold safety factor is unnecessary.

## 10. Fate and Ecotoxicity Assessment:

Acetic Acid and Salts

Acetic acid and its salts undergo dissociation in aqueous media at pHs commonly found in the environment to the acetate anion and the respective cations. The toxicity of each compound is driven by the acetate anion with the cations paying a minor role. Data suggest that acetic acid and its salts are not persistent in the environment.

The available ecotoxicity data indicate that these compounds are slightly to practically nontoxic on an acute basis.

Citric Acid and Salts

Similarly, citric acid and its salts also undergo dissociation in aqueous media in the environment to the citrate anion and the respective cations. The toxicity of each compound is driven by the citrate anion with the cations paying a minor role. The available information indicate that citric acid and its trisodium salt are readily biodegraded and modeling predicts that any citric acid released to the environment would partition to water. Therefore existing data indicates that citric acid and its salts would not be persistent in the environment.

The available ecotoxicity data indicate that these compounds are practically nontoxic on an acute basis.

Fumaric Acid

Fumaric acid is highly soluble in water and has low volatility. Virtually all the fumaric acid released to the environment would partition to water. Complete biodegradation would take approximately 21 days.

The available ecotoxicity data indicate that fumaric acid is slightly to practically non-toxic on an acute basis.

Malic Acid

Malic acid is highly soluble in water and has a low volatility. It is considered to be readily biodegradable in soil and water. Modeling predicts that any citric acid released to the environment would partition to water. Existing data indicates that malic acid salts would not be persistent in the environment.

Based on a limited amount of data and malic acid's structural similarities to the above chemicals, malic acid is likely to be practically non-toxic on an acute basis.

## 11. Fate and Ecotoxicity Characterization

A review of the readily available information on the chemical substances discussed in this document is sufficient to conduct a qualitative assessment of the potential exposures and risks associated with their use as pesticide inert ingredients. Environmental loadings are attributable to natural (plants and animal materials) and anthropogenic (food additives, drugs, and related products) sources. Available data indicate that they rapidly dissociate in the aquatic environment at environmentally relevant pHs to the corresponding acid (anion) and its respective cation. Anions of the respective compounds undergo aerobically mediated mineralization in days to weeks; mineralization is complete degradation to $CO_2$ and water. Mobility of the anions is expected to be high based on adsorption estimates, however, migration to ground water should be substantially mediated through their rapid biodegradation, volatilization, or through their uptake and utilization within plant cells.

**12. Cumulative Exposure:**

Section 408(b)(2)(D)(v) requires that, when considering whether to establish, modify, or revoke a tolerance, the Agency consider "available information" concerning the cumulative effects of a particular pesticide's residues and "other substances that have a common mechanism of toxicity." The citric acid cycle chemicals are structurally related; however, all are low toxicity chemicals. Therefore, the resultant risks separately and/or combined should also be low. EPA does not have, at this time, available data to determine whether these chemicals have a common mechanism of toxicity with other substances or how to include this pesticide in a cumulative risk assessment.

**13. IIFG Recommendations:**

By consensus there were no objections to the following:

The following tolerance exemptions are reassessed: In 40 CFR 180.2 citric acid and fumaric acid. In 40 CFR 180.1001 (c) acetic acid, calcium citrate, citric acid, potassium citrate, and sodium acetate. In 40 CFR 180.1001 (d) sodium citrate. In 40 CFR 180.1001 (e) acetic acid, citric acid, and potassium citrate.

The tolerance exemption for fumaric acid in 40 CFR 180.1001 (d) was inadvertently deleted and can be re-established.

Additionally, tolerance exemptions can be established for the potassium, calcium and magnesium salts of acetic acid and malic acid.

The following List reclassifications are made:

Acetic acid: Reclassified from List 4A to List 4B. Glacial acetic acid does not meet the criteria of

a List 4A. The original intent was to establish List 4A classification for Vinegar.
Vinegar (maximum of 8% acetic acid in solution): List 4A
Acetic acid: sodium, potassium, calcium, magnesium salts: List 4A
Citric acid: List 4A, to harmonize with its use as FIFRA 25(b) active ingredient
Citric acid: sodium, potassium, calcium, salts: List 4A
Malic acid : List 4A, to harmonize with its use as FIFRA 25(b) active ingredient
Fumaric acid: List 4A based on its similarities to malic and citric acid

Attachment:

EFED review (Abel; February 28, 2002)